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Case conference

Volunteers at risk

An experiment is described in which three male volunteers, who fully understood the nature of the project, were given doses of heroin which could have led to addiction if the subjects had proved to be physiologically or psychologically vulnerable to developing a state of addiction. The experiment was discussed most carefully by the Ethics Committee of the unit where it was conducted, and the subjects were themselves the investigators. The objective was to learn about the initial stages of the adaptation to heroin, of which nothing was known as heroin addicts usually come to the doctor when the habit is firmly established. A physician, who has studied the subject of drug addiction in a special clinic, is the first commentator, the second a lawyer and the third an associate professor of social ethics. These three experts are not discussing the results or the methodology of the experiment but whether the decision of the Ethics Committee was the right one.

Experimental design

An Ethics Committee was asked to advise on a project concerned with heroin abuse, a common contemporary cause of mortality in young people. Nearly all clinical, social and pharmacological studies on heroin addicts had inevitably been centred on those unfortunate individuals in whom the habit had already become established, and virtually nothing was known of the initial stages of adaptation to the drug. Retrospective accounts by addicts were clearly unsatisfactory, and in any case could not yield physiological data. The investigation was to help to remedy this defect, and in particular to study the effect of heroin on non-habituated individuals with particular reference to electroencephalographic changes. The senior investigator was an international authority on the effects of drugs on brain activity and on the mechanisms of addiction, drug withdrawal effects and drug adaptation, and had no difficulty in making out a cogent case, amply backed by references to the literature, demonstrating the potential usefulness of the knowledge it was hoped to obtain by the study.

The investigation itself called for heroin to be administered daily to three physically and mentally healthy male volunteers for two consecutive periods of five days with a brief interval between the courses. The dosage it was planned to use would usually be regarded as therapeutic, but there was no doubt that the quantities were quite sufficient to lead to heroin addiction if the subjects proved to be physiologically or psychologically vulnerable to developing an addiction state. The three subjects were fully aware of the hazards involved.

The Committee began by debating whether it was ethically justifiable to allow any individual, no matter how well informed, to engage in a study of this kind. There was no question of any possible benefit accruing to the participants, while on the other hand the risks of addiction, though not known, could not be assumed to be zero. The Committee's view at this stage was against endorsing the enquiry. Its main grounds for refusal were quite simply that it was unethical for anyone to be asked to volunteer to participate in a procedure which was potentially so dangerous, even if the risk for healthy individuals could not be precisely calculated, and whatever the potential gain to therapeutic or scientific knowledge.

A further unusual factor was that the three volunteers were themselves to be the investigators. The Committee were much exercised as to whether this altered the ethical situation. Despite some misgivings their final conclusion was that the experiment might proceed. The reasoning was that if an individual wished to hazard his life for the benefit of scientific knowledge, then his right to do so should be respected. Evidently he might permanently injure himself or even die. In the latter case, a loose analogy was discerned with the situation of an individual bent on suicide. While it may be unethical to assist an individual in any way to terminate his life, nevertheless if he were resolved to do so and was free of recognizable mental disorder at the time, then, as the law recognizes nowadays, one has no right to prevent his doing so. Members of the Ethics Committee are to this day wondering if they came to the correct conclusion.

In fact the experiment was then carried out, with the consequence that each of the three investigators found the heroin unpleasant, and suffered a good deal of nausea and malaise. None of them found the slightest pleasure in it and certainly had no wish to repeat their experience of the drug.

The work was duly published in scientific journals and was well received; the youngest investigator (subject) also submitted his section of the work as part of a PhD thesis which was successful.

Discussion

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The problem of research with drugs of dependence or potential dependence from the clinical, ethical and legal viewpoints has been one to which I have given some attention. Much of this contribution derives from an earlier one (Connell, 1973).

A general code of research ethics has been proposed in various reports (Declaration of Helsinki, 1964; MRC Annual Report, 1962–63; Royal College of Physicians Report, 1967). In particular, in relation to procedures not of direct benefit to the individual, the Medical Research Council (1962–63) notes that 'if he is to submit to it he must volunteer in the full sense of the word'. By 'true consent is meant consent freely given with proper understanding of the nature and consequences of what is proposed'.

Turning to the special case of the clinical evaluation of drugs a report of a scientific group (WHO, 1968) noted that 'good research should have a secure moral basis' . . . '. . . to evaluate ethical questions it is important to understand the objective and nature of the research'. That 'review of the purpose and design of the trial, and of preliminary data, by local research committees composed of physicians and experienced medical research workers ("peer groups") may actually be more effective than laws in protecting both the patient and the investigator'. It stated that rewards to encourage participation were acceptable but that it was necessary 'to ensure that rewards do not induce subjects to submit to unreasonable hazards, persons not involved in the research should review the protocol and decide the advisability of the study independently of considerations of reward'.

Few would doubt that the recommendations of the above reports should apply with particular force to research involving the use of drugs of known or suspected risk of dependency.

There are special problems and responsibilities when clinical practice and clinical research involves the use of drugs which have, or may have, a potential for producing drug dependence, whether on a physical or a psychological basis (or both). This is particularly true of new drugs which have not been shown in animal research to produce clear-cut dependency or in which the type of dependency does not conform to classical patterns of dependency produced by related substances.

In the past the test as to whether a drug has a dependency liability in humans has often been left to uncontrolled use of the drug, and to society to experiment and produce the problem rather than to the setting up of sound clinical scientific research on humans. This was partly due to the relative newness of the scientific method and of specialized techniques (for instance animal techniques) and to the time which is required for new methods to command widespread acceptance, and to train personnel in their use. An example of the uncontrolled social experiment was the use of amphetamines in the 1950s which were readily available in inhalers (containing 325 mg amphetamine base) and tablets, without a doctor's prescription, and which led to excessive dosage and to dependence and to the development of a drug psychosis (Connell, 1958).

There are a number of problems relating to the clinical use of drugs of dependence potential either for treatment or for research, particularly where the physical component of the dependence is minimal or apparently absent.

1) Although the large majority of persons who become dependent on such drugs have psychiatric problems or defects of personality, there is no guarantee that the 'normal' person will never, whatever the stress, become dependent on such drugs (Connell, 1970).

2) There is no known way of accurate evaluation as to which of the persons who have psychiatric problems or defects of personality (the vulnerable group) will, if exposed to risk, become dependent on such drugs. Many such persons who have had access to such drugs and have even tried them avoid becoming dependent on them.

3) Even if there were methods of assessing individuals in terms of their psychiatric and personality status in relation to defining accurately their liability to dependence, such procedures, at the present time, are lengthy and time-consuming, requiring comprehensive assessment of the individual, not only by the examination of the individual himself, but also by enquiry from other informants.

4) Studies on large numbers of 'normal' individuals carried out by physicians or others with no special training in the problems of drug dependence are unlikely to throw up significant numbers of individuals who show indisputable evidence of drug dependence for a number of reasons including a) because the numbers of vulnerable persons may be low; b) because, with the development of dependence, the individual may well decide to hide the dependence and try to obtain the drug (or a substitute) by other means.

5) An individual who has already shown dependence on one drug may well be more likely to manifest dependence on another drug and could, perhaps, be regarded as an 'expert' subject for research.

In the case of research on persons who have already been dependent on a drug, the question as to whether research using the same drug or another

drug will 'light up' drug dependence and to relapse into drug dependence, is relevant. In this respect Gotestam and Gunne (1972) used patients previously amphetamine addicts in a clinical drug trial, including the use of amphetamines, and showed that the first group (those who were given a single dose of amphetamines orally) did not differ in outcome from the control groups who had received no amphetamines. The second group (which took part in more extensive trials with amphetamines) had a better outcome than controls. Although the follow up was short (six months) it did suggest that there was no immediate lighting up of previous dependency patterns on account of participation in the clinical trial.

Finally, in this presentation, one must refer to the experience of US Army enlisted men in Vietnam (Robins *et al*, 1974). This comprehensive study of 943 men (900 were personally interviewed and urine specimens collected from 876) comprised 470 of the general population of Army enlisted men and 495 of those whose urines had been positive for opiates at the time of departure from Vietnam. Almost half of the 'general' sample had tried heroin or opium while in Vietnam and one-fifth developed physical or psychological dependence. In the period of eight to 12 months since return less than 1 per cent showed signs of opiate dependence. In the 'drug-positive' sample, three-quarters considered they had been addicted to narcotics but only 7 per cent showed signs of dependence at follow up. Although some sporadic use of opiates occurred in 10 per cent of the 'general' sample, and although there was a tendency to use other drugs in both samples, almost none expressed a desire for treatment. Thus, the popularly held belief that once dependent on opiates one is dependent for life, was shown to be a gross exaggeration of the state of affairs on follow up. Furthermore, the stresses of Vietnam could be considered to be far greater than the stresses met with in ordinary life situations and the risk of drug dependence in a random population in a normal life situation is likely to be very much smaller in terms of drug dependence.

Having introduced some of the problems in this field as a background to the 'case conference' which is concerned with a heroin research project, I would make the following observations:

1) Giving a drug with any potential for danger to healthy volunteers is a procedure which must be kept under strict ethical control. However, one must set against this the rights of the individual to make his own decision, having been acquainted with the facts.

2) Since the available evidence suggests that those with psychiatric disorder or personality disorders may be 'vulnerable' to the development of dependence, it is necessary to carry out a full psychiatric screen to evaluate the individual risk.

3) The fact that the volunteers were themselves the investigators in the study only has bearing in that the volunteers could be expected to be more sophisticated in their knowledge of the dangers. The fact that they wanted to do the research and wanted, perhaps, to publish a paper, might well neutralize the theoretical advantage of sophistication. I would not think that this really has much bearing on the general ethical position except that relating to the rights of any individual to take a risk. The comments made in 2 are just as relevant to these workers.

4) Although in terms of physical measurements (such as electroencephalographic) knowledge of the drug being used may be of no consequence; in terms of the risk of subsequent drug dependence it is wise for volunteers not to know what drugs are being used, so that if there is a pleasant effect the individual does not know what drug to look for. This secrecy is very difficult to arrange.

So far as the difficult problem faced by the Ethical Committee is concerned, it is my view that if the volunteers were taking part in such a research and did not know what drug was being used but were fully investigated in terms of psychiatric and personality problems, were over the age of 25 years and had the dangers explained in general terms (rather than specific to heroin), I would have considered the research to be ethical.

I would not consider it ethical to tell naïve volunteers that it was heroin that was going to be used, and include them in the research, since, although normal on full investigation, they might be one of the rare normal individuals (my belief) who may become dependent on the basis of psychological effects, and they would know what drug to look for. I would certainly not seek out volunteers for the kind of research described. If, however, by some entirely spontaneous and unsolicited way, volunteers sought out a research for no financial gain and found such a project, I would think they are in the same situation as the research workers and have the right to take risks. I cannot, however, see how such a situation could arise without some kind of coercion, overt or covert.

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The United Kingdom legislation governing dangerous drugs is clearly based on the view that in certain circumstances at least it is permissible to restrict the liberty of the individual in an attempt to enhance his safety and wellbeing. A particularly noticeable feature of the legislation, however, has always been the privileged and powerful position accorded to the medical profession – despite the fact that until fairly recently at least, a significant proportion of heroin addicts have been members of that profession. In 1959, for example, the major occupation of addicts was in medical and allied professions, and in 1923 regulations made under the Dangerous Drugs Act 1920 prohibiting the use of all controlled drugs for self administration were withdrawn following pressure from the medical profession which regarded the regulations as a limitation on their professional judgment. This shows that the profession possesses not only a privileged position, but also a powerful influence over the formulation of government policy and legislation in this area. This influence was again seen in operation in the mid-1950s when it successfully blocked a government attempt to ban heroin entirely. The profession's unique position should not be a matter either for surprise or criticism, because it is obvious that it possesses a repository of specialized knowledge and skills directed almost by definition towards the public good. Although the profession as a whole can no longer claim exclusive responsibility for the drug taker in view of successive restrictions on the right of doctors to prescribe heroin, it continues to possess a special authority which is still recognized by the law.

When the situation before us is seen against this general background, the natural first reaction is to commend the Ethical Committee for its careful efforts not to allow a privileged position to be abused. It is worth noting, however, that it exercised its discretion in a way quite contrary to the philosophy underlying the very legislation from which its discretion is ultimately derived. Unlike members of the general public, the investigators were allowed to risk becoming one of the 'walking dead'.

To describe a confirmed heroin addict in such terms may seem unduly melodramatic, but the Ethical Committee itself seems to have overdramatized the problem before it. There is, for example, a certain smugness in the view that 'if an individual wished to hazard his life for the benefit of scientific knowledge, then his right to do so should be respected'. The relevance of the motive is by no means self evident. Activities such as voluntarily undertaking a dangerous Army mission in Ulster, making an attempt on Mount Everest by a hitherto unclimbed route and leaping across the Grand Canyon on a motor cycle are in their own way all hazardous, but the right of the individual to pursue them is never seriously challenged.

In this connexion, the degree of hazard is surely all important. The soldier, climber or stuntman would say that the chances of injury or death can be much reduced by training, experience and reliable equipment. Thus while heroin is normally regarded as highly lethal, there is in fact little evidence that heroin *per se* is dangerous. The high mortality rate which the Committee had in mind is rather due either to overdose (where, for example, the addict does not realize the strength of his illicit purchase), infection (where the addict uses unsterile needles), the presence of adulterants (where, for example, the pusher dilutes his stock with talcum powder), or a combination of any or all of these. It was surely safe to assume that the investigators' experiments would be carried out in clinical conditions, thus substantially reducing the chances of an automatic and inevitable progression from the administration of a limited quantity of heroin to addiction, and eventually to death.

For this reason, the analogy (however loose) which the Ethics Committee drew with the person intending to commit suicide seems inappropriate. Otherwise, for the sake of consistency, the Committee should have based its first decision not to endorse an inquiry where the heroin would be administered to volunteers on the basis of a loose analogy with homicide.

Even on the assumption that the analogy with suicide was appropriate, it is wholly inaccurate and misleading to say that 'it may be unethical to assist an individual in any way to terminate his life', because to do so is not merely unethical but illegal. If suicide itself is not a crime then logically to assist a person to commit suicide should not be either, but a number of legal jurisdictions have perhaps rightly been reluctant to accept this con-

clusion. Thus to assist a known potential suicide by providing the poison, loading the gun or giving a 'leg up' onto the parapet of a bridge, for example, would result in criminal liability, as, of course, would administering the poison, firing the gun or giving the final push into the river, even if done at the victim's request.

The Committee clearly envisaged that a distinction could be drawn between 'assisting' a potential suicide on the one hand, and 'failing to prevent' him carrying out his intentions on the other. Obviously there are situations where such a distinction presents no difficulties. The failure to prevent a man jumping from a bridge, even if it lay within one's powers to do so, would not give rise to criminal liability, although it would be generally accepted that to stand idly by while a fellow human being voluntarily puts an end to his life would be not so much immoral as callous. But it is by no means clear that the distinction holds in the case of the problem before the Committee. It is reasonable to assume that the investigators were allowed to make use of the general facilities (laboratories and equipment, for example) provided by the institution of which both they and the Ethics Committee belonged, and which would almost certainly have been denied had the Committee decided not to allow the experiment to proceed. While this is not of course assistance of a direct nature, it does seem to extend beyond the limits of the quite negative 'failure to prevent'.

The Committee's reasoning is on the whole curious, and even at times misconceived. It is difficult to avoid completely the suspicion that the reasons given were not genuine, and that the investigators were permitted to go ahead because by virtue of their expertise they were able to make the most accurate assessment of the risks involved, and the Ethics Committee was tacitly deferring to the authority which the investigators possessed by virtue of that expertise. Admittedly this is mere speculation, but even if it is only partially correct it demonstrates the difficulties which bodies like the Ethics Committee must always face, and also, rather ironically, that the Ethics Committee (like Parliament in relation to drugs legislation) was accepting that there are effective limits to the exercise of formal and apparently absolute power.

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I will begin with my conclusions: 1) I would not consent to the participation of lay volunteers in the proposed heroin study; 2) I would consent to an initial study of the type proposed on one investigator-volunteer only, and further testing on investigator-volunteers would be dependent on the findings in the first case; 3) I would not permit participation of a student-investigator-volunteer.

Now to my reasoning. In my judgment, the risk of addiction outweighs the anticipated benefits of the study. Even though we might grant that the hoped for knowledge would be obtained, the benefits in terms of preventing or treating heroin abuse are not at all clear. The use of volunteers in high-risk experiments can only be justified by benefits that correspond to or exceed the degree of risk. Furthermore, the use of volunteers to test destructive effects of a dangerous agent may be distinguished from the use of volunteers to test therapeutic benefits of a dangerous agent. The separation of the experiments from the psychosocial setting of heroin abuse raises a further question about the usefulness of the experiment. I would not argue that lay volunteers can never risk serious injury or death, but the anticipated benefits do not appear to warrant the risk in this case.

To support my consent to participation by a single investigator-volunteer, I need to establish a distinction between types of volunteers in this type of study. The investigators have a very large advantage over the lay volunteers in understanding and appreciating the effects of heroin. Although informed consent is basic to clinical experimentation, there is always a question about how well a lay person will be informed. The investigators in the study presumably knew well the physiological effects, although they wanted more precision on timing and specific changes. The point is that I view the investigator as being in a distinctly advantageous position compared with a lay volunteer.

Perhaps more important than the above distinction, however, is the long tradition in medicine of self-experimentation. To the extent that established traditions represent distilled wisdom and accepted practice, they should be changed only when there is adequate cause. In this instance, although the potential risk is great, the situation appears to fall within an accepted pattern of self-experimentation.

The tradition has been established and sustained on the grounds that a knowledgeable investigator may observe more than a lay volunteer and the approval and acceptance by society of a sacrificial act by physician researchers. When the benefits are not clear or when the risk is very great the distinction between investigator and lay volunteer becomes determinative. It is important to note that the degree of risk is uncertain, but that fatality is not a certainty or even likely event. Although one cannot prevent suicide, an analogy used by the Ethics Committee, one is not required to consent to suicide and participate in it by providing the agent. If death (suicide) was certain, then the Ethics Committee could not consent.

I would assume that the risk of addiction is as great for an investigator as it is for a lay volunteer. The benefits would not necessarily be greater by

testing investigator-subjects, but it is possible that more precision in reporting effects might result. The major considerations for me, even if the results would be identical with either class of subjects, are the increased knowledge of the risks involved and the tradition of investigator participation in clinical studies.

The major change that the Ethics Committee should impose, in my judgment, is a limitation of approval to one subject. We are told that the Committee were 'much exercised'. Why, then, did they not determine that a proper course would be to minimize the risk by starting with one subject only? There would be no significant time delay and the results of the study would not be affected by staggering the administration. One subject would not be sufficient to determine the risk of addiction, but if signs of addiction or other adverse affects appeared, these would be adequate grounds for the Ethics Committee to refuse to sanction further testing.

I said that I would not permit participation of a student-investigator-volunteer. I am assuming that the graduate student was a student of the senior investigator or one of the other investigators. In my judgment, such a situation has too much chance for coercion, however subtle, to provide a clear case of voluntary consent. Students should not be prohibited from participation in all cases, but when the risks are very great they need protection by ethics committees. Certainly one can argue that all junior investigators, or even co-investigators, are subject to a degree of coercion. To me, students form a special class that needs special protection.

Finally, I wish to return to consideration of suicide as used in the process of decision by the Ethics Committee. We have only a brief summary of the discussion that occurred among Ethics Committee members, which may not do justice to the full discussion. In the summary, however, the tradition of the scientific investigator risking self for the benefit of scientific knowledge is justified in part by the 'loose analogy, to an individual bent on suicide'. The essential point is that one has no right to prevent an individual free of mental disorder from taking his own life.

The risk of serious injury or death may be borne in clinical experimentation if the potential benefits are great. The certainty of serious injury or death requires withholding consent from a proposed clinical experiment, no matter how great the potential benefits. An ethics committee is never required to assist an individual to commit suicide and in my judgment is acting unethically if consent is given when self destruction is knowingly sought by the subject. We never know with absolute certitude that a given individual will indeed go through with an announced suicide. To consent to a dangerous experiment on the basis that we cannot prevent suicide moves dangerously close to participation in the suicide.

The tradition of self-imposed risks by investigators in scientific investigations is strong enough to stand on its own. The inclusion of the suicide analogy weakens the force of the established tradition and moves the Ethics Committee away from the essential task of protecting subjects through assessing the risk-benefit ratio.